Remarks

Claims 49-56 were previously pending in the subject application. By this Amendment, claims 49-56 have been canceled, and new claims 57-67 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 57-67 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants wish to thank Examiner Wilson and Supervisory Examiner Reynolds for the courtesy of the personal examiner interview conducted on September 16, 2002 with the undersigned, Mr. David Saliwanchik, and Dr. John Sinden. The remarks and amendments set forth herein are consistent with the substance of that interview and are believed to address the outstanding issues as discussed during the interview.

The Office Action suggests that the first line of the subject specification may need to be updated if the subject application is a continuation-in-part of U.S. patent application Serial No. 09/672,606 (hereinafter the '606 application). However, as indicated below, the disclosure of the subject application is identical to that of the '606 application. Therefore, the subject application is a continuation of the '606 application. Therefore, page 1 of the specification correctly describes the relationship between the subject application and the domestic priority documents.

Claims 52-56 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicants respectfully submit that the subject specification as originally filed fully describes the subject matter of the claimed invention. However, as indicated above, the applicants have canceled claims 49-56, rendering moot this grounds for rejection.

Please note that support for new claims 57-67 can be found throughout the subject specification as originally filed. Claim 57 recites a method of treating a cognitive deficit in a mammal by intracerebrally transplanting pluripotent, nestin-positive, neuroepithelial cells, wherein the cells have been genetically modified to be conditionally immortal, wherein the cells are immortal prior to transplantation but differentiate after transplantation, and wherein transplantation of the cells improves cognitive function in the mammal. Intracerebral transplantation of conditionally immortal cell lines is described in Examples 6-9 at pages 24-29 of U.S. application Serial No. 09/043,061

(hereinafter the '061 application) and the '606 application, as well as the subject application as originally filed. Furthermore, as described in Example 4 at page 20, lines 27-36, and page 21, lines 1-8, of the '061 and '606 applications, as well as the subject application as originally filed, these cells express the marker nestin under both permissive conditions (33° C) and nonpermissive conditions (39° C). Thus, these cells were nestin-positive prior to transplantation, as recited in claim 57. Written support for administration of cells to treat a cognitive deficit in a mammal with resulting improvement in cognitive function can be found at page 9, lines 30-36, and page 10, lines 1-36, of the '061 and '606 applications, as well as the subject application as originally filed. Specific support for intracerebral transplantation of the cells can be found, for example, at page 14, lines 29-32, of the '601 and '606 applications, as well as the subject application as originally filed. Written support for the cells' immortality prior to transplantation and differentiation subsequent to transplantation can be found, for example, at page 5, lines 32-36, page 6, and page 7, lines 1-7, of the '061 and '606 applications, as well as the subject application as originally filed. Specific support for "genetic modification" to confer conditional immortality can be found at page 14, lines 9-11, of the '061 and '606 applications, as well as the subject application as originally filed. Written support for the cells' pluripotency can be found, for example, at page 1, lines 25-36, and page 2, lines 1-10, of the '061 and '606 applications, as well as the subject application as originally filed. Written support for claim 58 can be found, for example, at page 14, lines 5-6, of the '061 and '606 applications, as well as the subject application as originally filed. Written support for claim 59 can be found, for example, at page 20, lines 18-25, of the '061 and '606 applications, as well as the subject application as originally filed. Written support for claims 60 and 61 can be found at page 17, lines 21-36, page 18, and page 19, lines 1-32, of the '061 and '606 applications, as well as the subject application as originally filed. Written support for claim 62 can be found at page 2, lines 35-36, of the '061 and '606 applications, as well as the subject application as originally filed. Written support for claims 63 and 64 can be found at page 2, lines 14-24, of the '061 and '606 applications, as well as the subject application as originally filed. Written support for claims 65-67 can be found, for example, at page 5, lines 32-36, page 6, page 7, lines 1-7, page 9, lines 1-15, and page 12, lines 10-23, of the '061 and '606 applications, as well as the subject application as originally filed.

Thus, the claims as currently presented are fully described and enabled by the specification as filed. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection set forth under 35 U.S.C. §112, first paragraph.

Claims 49-56 have been rejected under 35 U.S.C. §112, first paragraph, as being non-enabled. The applicants respectfully traverse this grounds for rejection because a person skilled in the art, having the benefit of the applicants' disclosure, could readily practice the claimed invention without undue experimentation.

As discussed during the personal Examiner interview, the Office Action raises issues as to the enablement of the following aspects of the claimed method: (1) the types of cells or tissues to be treated; (2) the types of cells to be transplanted; (3) the types of animals to be treated; and (4) the types of conditions to be treated. The applicants respectfully submit that claims 57-67 are fully enabled by the subject specification. Accompanying this Amendment is an Expert Declaration under 37 C.F.R. §1.132 by Dr. John Sinden. In his expert declaration, Dr. Sinden directly addresses the technical issues raised by the Examiner in the outstanding Office Action.

I. Types of cells or tissues to be treated

Citing the Scheffler *et al.* publication (1999), the Office Action indicates that the state of the art at the time of filing was such that it was unpredictable how to target particular areas of the brain when transplanting neural cells. As indicated in Dr. Sinden's Expert Declaration, "one of the great advantages of the present invention is that it is not necessary to target particular areas of the brain to correct cell damage." This is emphasized at various points throughout the subject specification, as well (see, for example, page 5, lines 10-31).

As Dr. Sinden explains in his Declaration, "[p]reviously, it was thought that to treat damage in a developed postnatal or adult brain, it was necessary to use tissue/cells derived from the same area as that damaged. Importantly, prior to our invention, even if the cells to be transplanted were taken from a fetus, such as those described in the Netto *et al.* publication, the cells would typically be committed to a particular phenotype. Moreover, prior to our work, there was no selection of nestin-positive, pluripotent cells, or genetic modification of the cells to confer conditional immortality such that the cells would be immortal prior to transplantation but differentiate subsequent to transplantation." In contrast, the inventors of the subject application realized that, "surprisingly,

transplanting cells that were selected to retain a nestin-positive, pluripotent, conditionally immortal phenotype resulted in the repair of damage, and this was independent of the site of damage", as indicated in Dr. Sinden's Declaration.

Accordingly, using the methods of the claimed invention, it is now possible to treat different sites of damage with one cell line, which is selected on the basis of its nestin-positive, pluripotent characteristics, and is genetically modified to be conditionally immortal.

In contrast to the observations made in the Scheffler *et al.* publication, as stated above, the applicants respectfully submit that the targeting of cells is not necessary using the methods of the subject invention. The subject specification teaches that the cells migrate to areas of damage after transplantation, and become integrated in the damaged areas, effecting repair. As explained by Dr. Sinden in his Declaration, "[t]his ability of the cells to migrate (which we were the first to observe) is an inherent feature of the cells; therefore, the difficulties identified in the Scheffler *et al.* publication will not be experienced when using nestin-positive, pluripotent neuroepithelial cells that have been genetically modified to be conditionally immortal."

Submitted with Dr. Sinden's Declaration as Exhibit B is a copy of U.S. Patent Application Publication No. 2002/0037277. The example at pages 2-5 of the application clearly demonstrates the migration of the cells, and also shows that cells from one region of the brain (hippocampal region) can repair damage to a different area of the brain, such as cortex and basal ganglia. The cells utilized in the example are nestin-positive, pluripotent neuroepithelial cells that have been genetically modified to be conditionally immortal, as recited in the currently pending claims. As indicated by Dr. Sinden in his Declaration, "[c]ompelling evidence of extensive migration is presented at page 4, paragraph 0047, which indicates that contralaterally grafted cells 'migrated across the midline to the opposite side of the brain (emphasis added)'."

II. Types of cells to be transplanted

The applicants respectfully submit that, given the benefit of the applicants' disclosure, a person skilled in the art could readily identify and use nestin-positive, pluripotent neuroepithelial cells as claimed. Evidence of the ability to use a variety of cells to treat various tissues is provided within Exhibit D, which accompanies Dr. Sinden's Declaration. Exhibit D details an experiment carried out using human nestin-positive pluripotent neuroepithelial cells derived from the human

fetal cortex, to treat damage associated with the basal forebrain. These cells were genetically modified to be conditionally immortal, as recited in the currently pending claims.

It should also be noted that although the cells transplanted into the brain may populate non-damaged areas, this is not detrimental to the patient. The important feature is that the cells do populate the damaged areas, and this overcomes the difficulties highlighted by Scheffler *et al.*, relating to the use of differentiated neurons in transplantation.

Sinden *et al.* (1997) has been cited in the Office Action as suggesting that CA1 cells derived from the hippocampus must be used to repair damaged CA1 tissue. The applicants submit that the cited portion of the Sinden *et al.* (1997) reference is merely characterizing the prior art. As indicated in Dr. Sinden's Declaration, "[t]he statement referred to by the Reviewer within the Sinden *et al.* publication (of which I am the first author), is made with respect to a previous study that used primary cells that were mature, differentiated or committed CA1 cells, and not the conditionally immortal, pluripotent, nestin-positive, neuroepithelial cells that are used in the method of our invention" (emphasis added).

As indicated in Dr. Sinden's Declaration, "[p]rovided the neuroepithelial cells are nestin-positive and retain the ability to differentiate into the specified phenotypes in response to environmental signals, they are appropriate for use in the present invention." The Scheffler *et al.* publication does not provide any reason to doubt that one of ordinary skill in the art, having the benefit of the applicants' disclosure, can determine what is, and what is not, an appropriate pluripotent neuroepithelial stem cell for use in the method of the subject invention. Furthermore, as discussed during the personal examiner interview, the neuroepithelial cells recited in new claims 57-67 are also positive for the progenitor cell marker, nestin. As indicated in Dr. Sinden's Declaration, "[n]estin-positive cells can be readily identified using immunocytochemistry," as described at pages 20 and 21 of the subject patent application, or by other techniques known to those of ordinary skill in the art. Thus, the applicants respectfully submit that the subject specification provides adequate guidance for the skilled person to identify and use appropriate cells.

The Office Action also indicates that the subject specification does not provide sufficient guidance for conferring conditional immortality to cells. As indicated above, new claims 57-67 recite that the cells have been genetically modified to be conditionally immortal, wherein the cells

are immortal prior to transplantation but differentiate after transplantation. As taught in the specification, such conditionally immortal cells can be readily prepared by transduction of an oncogene into a cell (see, for example, page 6 of the specification). Conditional immortality is described on page 5, last paragraph, and pages 6 and 7 of the specification, and it is clear that the cells remain immortal (undifferentiated and continuously dividing) under one set of conditions, but can be induced to mature and differentiate (losing immortality) by a change in conditions. Submitted herewith is the Frederiksen *et al.* publication, which shows that methods for achieving conditional immortality using, for example, the temperature-sensitive SV40 oncogene, were known in the art even in 1988. Therefore, the applicants respectfully submit that the subject specification fully enables the intracerebral transplantation of cells that have been genetically modified to be conditionally immortal, as recited in the currently pending claims.

III. Types of animals to be treated

New claims 57-67 recite methods for treating a cognitive deficit in mammals. The applicants respectfully submit that the animal model exemplified in Examples 5-9 of the subject application is predictive of the applicability of the claimed method to other mammals, including humans.

The Office Action refers to Sanberg *et al.* (*Proc. of the 1998 Miami Biotechnology winter symposium*, Feb. 1998, 38:139-142) as teaching that human fetal transplantation of human pluripotent neuroepithelial cells may result in poor graft survival and that immunosuppressive agents used for xenotransplanted cells may preclude any therapeutic benefit in humans because of the health risks associated with immunosuppression. As explained in Dr. Sinden's Declaration, "in all forms of transplantation therapy, *e.g.*, liver, heart, *etc.*, immuno-suppressive agents are virtually always included as part of the treatment regimen to help avoid rejection."

Please note that data has now been obtained confirming the efficacy of the pluripotent cells in treating primates, including marmosets and humans. In experiments described by Virley *et al.* (1999), pluripotent MHP36 cells (mouse cells exemplified in the subject application) were administered to the brains of marmosets (a primate). As indicated in Dr. Sinden's Declaration, "[t]hese cells performed as well within the marmoset brain as the marmoset fetal allografts, which suggests a low immune response provocation" (see paragraph bridging pages 111-112 of the Virley *et al.* publication).

Please note that the Virley *et al.* publication is submitted herewith simply to confirm the accuracy and sufficiency of the disclosure as set forth in the applicants' specification as filed. As indicated in Dr. Sinden's Declaration, the experimental data described in the Virley *et al.* publication confirms the applicability of the claimed methods to primates in general, including humans, with a reasonable expectation of success.

As the Examiner is aware, the determination of enablement must be based on evidence as a whole. As indicated in MPEP § 2164.05, "the evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art ... A declaration or affidavit is, itself, evidence that must be considered" (emphasis in original). MPEP § 2164.05 states:

> To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.

Further evidence of the versatility of the claimed methods to treat mammals is provided in Exhibit D, which describes an experiment using human nestin-positive pluripotent neuroepithelial cells to treat damage within the brain of a rat.

With regard to the comments concerning the Morris water maze test set forth at pages 6 and 7 of the Office Action, the applicants submit that those of ordinary skill in the art could readily envision and utilize other tests to assess the restoration of cognitive function in various mammals. For example, in the experiments on marmosets described in the Virley *et al.* publication, the Wisconsin General Test Apparatus was utilized (see page 104, first column, of Virley *et al.*). In the case of humans, tests that make use of motor and/or verbal output can be utilized. As the Examiner is aware, MPEP § 2164.05(a) states that "the specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public (emphasis added). *In re Buchner*, 929 F 2. 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

The Office Action cites various documents as evidence for the lack of long-term success in human gene therapy. It should be understood that the claimed invention is not concerned with gene therapy. The cited documents relate to the problem of how to target genes to particular cells/tissues

in vivo. Although the cells utilized in the claimed method may be genetically modified, the processes by which this may be carried out are well established. For example, the cells can be transduced with a temperature-sensitive oncogene *in vitro* and subsequently implanted into a patient, as described in the subject application. The claimed method does not require delivery of exogenous nucleotides into cells *in vivo*.

IV. Types of conditions to be treated

The Office Action indicates that the specification does not provide adequate guidance to treat "any behavioral or psychological deficit". As indicated above, new claims 57-67 recite a method of treating a cognitive deficit by intracerebral transplantation of nestin-positive, pluripotent, neuroepithelial cells, resulting in improvement of cognitive function, which is consistent with the claim language discussed at the personal examiner interview.

As indicated by Dr. Sinden in his Declaration, "[t]he Morris water maze test was developed in the 1980s and has become the method of choice for assessment of spatial learning and memory in rodents. The test is also accepted by those skilled in the art as generally predictive of long-term neurological and behavioral outcome in humans and is routinely utilized in the development of repair strategies for human neuro-degenerative disorders. This is evidenced by the enormous number of publications in the field in which this model is utilized. A survey of the literature shows a general consensus that the water maze test is useful in assessing cognitive function (*e.g.*, spatial learning and memory) within the context of a variety of etiologies (*e.g.*, aging, neonatal stress, lesion or ischemic damage to cortex, striatum, or hippocampus) and treatments (Morris R.G.M. "Spatial localisation does not require the presence of local cues" *Learn Motiv.*, 12: 239-260, 1981; Rapp. P.R. *et al.* "An evaluation of spatial information processing in aged rats" *Behav. Neuroscience*, 101:3-12, 1987; Di Mattia R. and Kesner P. "Spatial cognitive maps: differential role of parietal cortex and hippocampal formation" *Behav. Neuroscience*, 102:471-480, 1988; Stewart C.A. *et al.* The water maze. In Behavioural Neuroscience: a practical approach, Rickwood D and Hames H.D. (eds), Oxford. OUP, pp106-122, 1993; Propoli P. *et al.* Behavioural and electrophysiological correlates of the quinolinic acid lesion model of Huntington's Disease in rats, 1994; Hodges H. Testing for spatial brain dysfunction in animals. In: *Handbook of Spatial Learning,* eds N. Foreman and R. Gillett, Chapter

15, 1998; McIlwain, Merriweather M.Y. *et al.* "The use of behavioural test batteries: effects of training history" *Physiol and Behav.*, 73:705-17, 2001)."

The Wisconsin General Test Apparatus was utilized to assess cognitive function in the experiments on marmosets in the Virley *et al.* publication. As indicated by Dr. Sinden in his Declaration, "[t]he Wisconsin General Test Apparatus has been consistently used world wide for testing cognitive function in primates at least since the 1940s, across a range of species including Rhesus, Cynomolgus, and Squirrel monkeys, and marmosets, as demonstrated by the Harlow publication (Harlow, H.F., "A test apparatus for monkeys", *Psychological Record*, 2, 434-436, 1938), and subsequent publications (Harlow, H.F., "The formation of learning sets", *Psychol. Rev.*, 56:51-65, 1949; Ridley, R.M. *et al.*, "A new approach to the role of noradrenaline in learning: problem-solving in the marmoset after alpha-noradrenergic receptor blockade", June, 14(6):849-855, 1981; Ridley R.M. *et al.* "Cholinergic learning deficits in the marmosets produced by scopolamine and ICV hemicholinium" *Psychopharmacology* 83, 340-345, 1984; Roberts, A.C. "Comparison of cognitive function in human and non-human primates" *Cognitive Brain Res.* 3, 319-327, 1996; and Ridley R.M., and Baker HF "Evidence for specific information processing in monkeys with lesions of the septohippocampal system" *Cortex* 33, 167-76, 1997."

The applicants respectfully submit that, in view of the disclosure of the subject specification as originally filed, and in view of experimental data subsequently developed using those techniques described in the specification and known to those of ordinary skill in the art, treatment of a cognitive deficit is fully enabled.

In view of the above remarks, amendments to the claims, and the documents submitted herewith, the applicants respectfully submit that the pending claims are fully enabled by the subject specification as filed and, therefore, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 49-56 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. The Examiner has objected to the use of certain phrases in the claims. The applicants appreciate the Examiner's careful review of the claims. In order to expedite prosecution and to lend greater clarity to the claimed subject matter, the applicants have cancelled claims 49-56 and added new claims 57-67. New claims 57-67 either do not recite the phrases to which the Examiner has objected, or

include further clarifying language. For example, the applicants submit that the term "conditionally immortal" is both recognized in the art and is defined at pages 5-7 of the subject specification; however, in order to lend further clarity to the term, new claim 57 recites that the cells are immortal prior to transplantation but differentiate after transplantation. In addition, the Office Action indicates that the metes and bounds of the phrase "pluripotent cells having neuronal and glial potential", which was recited in claim 52, cannot be determined. New claim 59 recites that the nestin-positive, pluripotent neuroepithelial cells differentiate into neurons and glial cells *in vivo*. The Office Action indicates that the phrase "wherein said transplanted cells migrate and differentiate to replace, or compensate for, said lost or damaged brain cells", which was recited in claim 52, is unclear. New claim 58 recites that the transplanted cells differentiate to replace or compensate for lost or damaged brain cells. The Office Action indicates that the metes and bounds of the phrase "cells from a clonal cell line", which was recited in claim 55, cannot be determined. New claim 60 recites that the nestin-positive, pluripotent neuroepithelial cells are cells of a clonal cell line.

Accordingly, in view of the foregoing remarks and amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection set forth under 35 U.S.C. §112, second paragraph.

Claims 49-56 have been rejected under 35 U.S.C. §102(b) as being anticipated by Netto *et al.* (*Behavioral Brain Res.*, 1993, 58:107-112). The applicants respectfully traverse this rejection because the cells used by Netto *et al.* do not have the critical advantageous characteristics of the cells used in the applicants' method.

The cells described in the Netto *et al.* publication are not pluripotent cells that have been genetically modified to be conditionally immortal so as to differentiate after transplantation, as recited in the currently pending claims. Specifically, as described at page 1, lines 24-36, and page 2, lines 1-10 of the specification, pluripotent cells are undifferentiated cells that have the capability to differentiate into multiple cell types. As explained at page 13, lines 7-18, of the subject specification,

> if pluripotent cells are desired then the cells must, however, be taken at a point early enough in the developmental pathway that they have the ability to differentiate into the desired variety of different types and/or phenotypes of brain cell types. For example, in the case of cells taken from the embryonic mouse hippocampus the cells may be taken on embryonic day 14 to 15. Human cells may be taken at the

equivalent developmental stage. For example, cells may be taken from human fetuses at about 8 weeks.

As explained by Dr. Sinden in his Declaration, the Netto *et al.* publication "describes the transplantation of CA1 cells from late fetal stages, *e.g.*, embryonic day (E) 19-20; these cells are typically mature, differentiated cells and hence not pluripotent or nestin-positive." Please note that Dr. Sinden is one of the authors of the Netto *et al.* paper.

In order to anticipate under 35 U.S.C. §102, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991). The applicants respectfully submit that the Netto *et al.* publication does not teach or suggest every element of the applicants' claimed method and, therefore, does not anticipate or render obvious the claimed invention.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 49-56 have been rejected under 35 U.S.C. §103(a) as being obvious over Netto (*Behavioral Brain Res.*, 1993, 58:107-112) in view of Bernard (U.S. Patent No. 5,580,777) and further in view of Rashid-Doubell *et al.* (*Gene*, 1994, 1(1):S63). The applicants respectfully traverse these grounds for rejection because the cited references, alone or in combination, do not disclose or suggest the claimed invention.

The shortcomings of the Netto *et al.* reference have been discussed above. The Bernard *et al.* and Rashid-Doubell *et al.* references do not cure the defects of the Netto *et al.* reference.

There is no description in the Bernard *et al.* patent of cells that have been genetically modified to be conditionally immortal, as recited in the currently pending claims. Rather, the cells are transduced with the C-myc oncogene, which results in cells that are permanently immortal thereafter.

The applicants respectfully submit that it would not have been apparent to the skilled person to combine the teachings of the Netto *et al.* publication and the Rashid-Doubell *et al.* publication, to arrive at the claimed invention. As explained above, Netto *et al.* used more mature cells (taken at embryonic days 19-20) that were not genetically modified to be conditionally immortal so as to

differentiate after transplantation, as recited in the currently pending claims. Because it was believed at the time that committed or differentiated cells were required to treat damage, and that the cells for transplantation should be derived from the same area of the brain to be treated, there was no motivation to combine these references to arrive at the current invention.

The Rashid-Doubell *et al.* publication describes the preparation of pluripotent neuroepithelial cells that are genetically modified by the introduction of the temperature-sensitive SV40 T antigen gene. However, the Rashid-Doubell *et al.* publication does not propose using the cells for therapy or suggest that such cells would be suitable for transplantation into a damaged brain. The teaching in the Rashid-Doubell *et al.* publication is of an *in vitro* culture of pluripotent neuroepithelial cells used to study cell division and differentiation with different growth factors. Accordingly, there is no motivation for the skilled person to depart from the teaching of the primary reference, the Netto *et al.* publication. Thus, there would be no motivation to transplant nestin-positive, pluripotent (as opposed to differentiated) neuroepithelial cells that have been genetically modified to be conditionally immortal, as recited by the currently pending claims. Neither the Netto *et al.* nor Rashid-Doubell *et al.* publications indicate that transplantation should be carried out using anything other than committed cells.

Thus, there is no suggestion or motivation in the prior art that would lead a person skilled in the art to arrive at the current invention. As a matter of law, a finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, it is only the applicants' disclosure that provides such a teaching, and the applicants' disclosure cannot be used to reconstruct the prior art for a rejection under §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

There mere fact that the purported prior art could have been modified or applied in a manner to yield applicants' invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art. . . ." *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531, (Fed. Cir. 1988). In the references cited in support of the §103 rejection, one finds neither.

The benefits of the present invention, such as the ability of these cells to migrate to sites of damage, and the ability to use one type of cell line to treat damage in different areas of the brain, would not have been apparent to the skilled person from any of the prior art documents, individually, or in combination. Therefore, the applicants respectfully submit that the cited references, either alone or in combination, do not teach or suggest the applicants' claimed invention.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachments: Petition and Fee for Extension of Time
Declaration by Dr. Sinden under 37 C.F.R. §1.132, including Exhibits A-D
Frederiksen *et al.* (1988) publication